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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,457	11/30/2005	Caroline Connolly	FDEHN7.001APC	5613

20995 7590 02/20/2009

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EXAMINER	
SCHUBERG, LAURA J	

ART UNIT	PAPER NUMBER
1657	

NOTIFICATION DATE	DELIVERY MODE
02/20/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/520,457	CONNOLLY ET AL.	
	Examiner	Art Unit	
	LAURA SCHUBERG	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 14-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 14-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/26/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is responsive to papers filed 11/26/2008. Claims 8-13 have been canceled. New claims 16-29 have been added. No claims have been amended.

Claims 1-7 and 14 -29 are pending and have been examined on the merits.

Response to Arguments

Applicant's arguments filed 11/26/2008 have been fully considered but they are not persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Applicant argues that while Kraus does disclose that virus inactivation can be undertaken before or after thrombin is isolated, there is no disclosure or suggestion that virus inactivation could be carried out on prothrombin. Applicant asserts that this is consistent with the knowledge in the art at the time that virus inactivation using solvent/detergent should be carried out after the prothrombin has been activated to form thrombin because phospholipids, which are necessary for the activation reaction, would be eliminated by the S/D treatment. Applicant asserts that the skilled person reading Kraus would not have expected that S/D virus inactivation could in fact be carried out before the prothrombin was activated to form thrombin.

This is not found persuasive because Kraus never states that the S/D treatment can not be carried out on the prothrombin. Kraus suggests that the timing of the S/D treatment is flexible and can be accomplished by treating the plasma or plasma fractions either before or after the thrombin is isolated. In addition, with regard to the S/D treatment of prothrombin prior to activation to thrombin, there are several examples in the prior art wherein this has shown to be possible. Ralston et al (US 6,245,548) teach a method wherein prothrombin undergoes S/D treatment prior to activation to thrombin (columns 3-4, example 1).Metzner et al (US 7,351,561) also teach wherein prothrombin can be subjected to virus inactivation by known methods and then activated into thrombin (column 2 lines 61-67). Karges et al (US 5,723,123) also teach that a prothrombin complex that has been virus inactivated in any suitable way may then be activated to a virus-free thrombin (column 2 lines 12-30). Clearly, treating prothrombin to a well known virus-inactivation treatment, such as S/D, prior to thrombin activation is not considered unfavorably by all those of ordinary skill in the art at the time of the invention as Applicant asserts.

Applicant argues that Anderle does not teach that S/D treatment can be used to inactivate viruses in a prothrombin complex prior to loading onto an anion exchange medium.

This is not found persuasive because Anderle et al specifically teach that the protein may be purified either before or after the enrichment treatment (page 5 para 58). Clearly Anderle et al teach that the order of the steps is flexible with regard to the purification and enrichment of the proteins.

Applicant argues that the knowledge in the art at the time of the invention was that phospholipids were required for the activation of prothrombin to thrombin. Applicant cites the teachings of Dr. Karl Landsteiner described in Applicant's specification as evidence of this teaching. Applicant asserts that those of skill in the art at the time of the invention would have required the addition of phospholipids for prothrombin that had been subjected to S/D treatment.

This is not found persuasive because, as discussed above, Ralston et al, Metzner et al and Karges et al suggest the virus-inactivation of prothrombin prior to activation and do not state that the addition of phospholipids is required. Clearly, the specific protocol for S/D virus-inactivation determines whether additional phospholipids are required or not.

Applicant argues that the present invention provides significant unexpected results as compared to the Kraus method. Applicant asserts that the presently claimed invention provides both a purity and concentration of thrombin which are surprisingly better than those achieved by the Kraus reference.

This is not found persuasive because one of ordinary skill in the art would expect to gain improved results for the Kraus et al method by adding the purification method of Anderle et al. Anderle et al state that their protein purification method has surprisingly shown that pathogens in a protein solution are effectively inactivated, while the protein activity is substantially preserved (page 2 para 14). In addition, the examples that Applicant cites as evidence for unexpected results (examples 1 and 14) include additional elements that are not included in the invention as claimed and are therefore

not commensurate in scope. In addition, the starting amounts used for the methods would appear to affect the yield produced as well and should be taken into consideration.

In submitting evidence asserted to establish unobvious results, there is a burden on an applicant to indicate how the examples asserted to represent the claimed invention are considered to relate to the examples intended to represent the prior art and, particularly, to indicate how those latter examples do represent the closest prior art. See *In re Borkowski*, 595 F.2d 713, 184 USPQ 29 (CCPA 1974); *In re Goodman*, 339 F.2d 228, 144 USPQ 30 (CCPA 1964).

The evidence relied upon should also be reasonably commensurate in scope with the subject matter claimed and illustrate the claimed subject matter "as a class" relative to the prior art subject matter "as a class." *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971); *In re Hostettler*, 429 F.2d 464, 166 USPQ 558 (CCPA 1970). See, also, *In re Lindner*, 457 F.2d 506, 173 USPQ 356 (CCPA 1972).

It should also be established that the differences in the results are in fact unexpected and unobvious and of both statistical and practical significance. *In re Merck*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); *In re Longi*, 759 F. 2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Klosak*, 455 F2d 1077, 173 UAPQ 14 (CCPA 1972); *In re D'Ancicco*, 429 F.2d 1244, 169 USPQ 303 (CCPA 1971). *Ex parte Gelles*, 22 USPQ2d 1318 (BPAI 1992).

Applicant asserts that the Examiner incorrectly describes Kraus's ultrafiltration step as purification when it is actually a concentration step.

In fact, the Examiner was referring to the statement by Kraus "filtered sterile" (column 2 line 61) which indicated filtering for increased purity as well.

A showing of unexpected results that is commensurate in scope with the claims and that clearly compares the claimed method with the prior art methods "as a class" might be able to overcome the obviousness rejections below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 14, 16-19, 21-24, 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kraus et al (US 5,143,838) in view of Anderle et al (US 2003/0133829).

Claim 1 is drawn to a method for the preparation of virus-inactivated thrombin comprising a) solvent-detergent virus inactivating of a solution comprising prothrombin and factor X; b) loading the product of step a) onto an anion exchange medium; c) washing the anion exchange medium to remove reagents used for step a); and d) activating the prothrombin on the anion exchange medium to form thrombin by addition of metal ions.

Dependent claims include wherein the solution is prothrombin complex (claim 2), the type of metal ions (claims 4 and 5), further comprising the steps of e) selectively eluting the thrombin from the anion exchange medium (claim 6) and wherein step d is performed without the addition of phospholipids (claims 26).

Claim 3 is drawn to a method for the preparation of virus-inactivated thrombin comprising a) solvent-detergent virus inactivating of a solution comprising factor X; b) loading the product of step a) onto an anion exchange medium; c) washing the anion exchange medium to remove reagents used for step a); and d) activating the factor X on

the anion exchange medium to form factor Xa by addition of metal ions; and e) loading virus-inactivated prothrombin onto the anion exchange medium such that thrombin is generated.

Dependent claims include the type of metal ions (claims 4 and 5), replacing steps a) and b) with steps a') and b') wherein a') is loading a solution comprising prothrombin and factor X onto an anion exchange medium and b') is solvent-detergent virus inactivating of the prothrombin and factor X on the anion exchange medium (claim 8), further comprising the step of f) selectively eluting the thrombin from the anion exchange medium (claim 14) and wherein step d is performed without the addition of phospholipids (claims 27).

New claims 16 and 21 are drawn to a method for the preparation of virus inactivated thrombin comprising replacing steps a) and b) with steps a') and b') wherein a') is loading a solution comprising prothrombin and factor X onto an anion exchange medium and b') is solvent-detergent virus inactivating of the prothrombin and factor X on the anion exchange medium (previous claim 8), wherein claim 16 requires activating prothrombin in step d and claim 21 requires activating factor X in step d.

Dependent claims include the type of metal ions (claims 17, 18, 22, 23), further comprising the steps of e) selectively eluting the thrombin from the anion exchange medium (claims 19 and 24) and wherein step d is performed without the addition of phospholipids (claims 28-29).

Kraus et al teach a method of producing thrombin from prothrombin using calcium ions for the conversion on an anion exchange medium. The includes a solution,

preferably human blood plasma or a fraction thereof, that contains Factor II (prothrombin) is adsorbed onto an anion exchange medium (column 2 lines 26-36). For elution a buffer that contains an activator –calcium ions, calcium ions plus thromboplastin or Factor Xa are applied to the matrix. The plasma or plasma fraction is activated into thrombin with the buffer solution by eluting the matrix (column 2 lines 37-49). Filtration of the thrombin is suggested and taught to increase purity (column 2 lines 58-61). Before or after the thrombin is isolated from the plasma or plasma fraction the batch can be sterilized to inactivate human-pathogenic viruses by treatment with detergent or by heating (column 3 lines 1-7). Phospholipids are not taught to be required.

Kraus et al do not teach solvent-detergent inactivation on the anion exchange medium or freeze-drying the thrombin product.

Anderle et al teach a process for inactivating pathogens in a biological material. The solvent-detergent virus inactivating of a protein solution, the subsequent adsorption to an anion exchange medium (DEAE sephadex), washing of the protein loaded anion exchange medium, elution of the proteins and filtration are taught (pages 7-8, examples 4 and 7). In addition to protein enrichment steps, the protein may also be purified either before or after the treatment disclosed (page 5 para 58). Exemplary proteins include coagulation factors such as FII (prothrombin) and FX and FEIBA (activated prothrombin complex concentrate) (page 5 para 57 and page 6 para 66). The method is taught to be a gentle, effective procedure for inactivating pathogens in a protein solution, which does

not substantially reduce the activity of a selected protein in the solution (page 2 para 12).

Therefore, one of ordinary skill in the art would have been motivated to apply the solvent-detergent inactivating steps of Anderle et al to the method of Kraus et al because Anderle et al teach that these steps are a gentle, effective procedure for inactivating pathogens in a protein solution, which does not substantially reduce the activity of a selected protein in the solution (page 2 para 12) and Kraus et al had also suggested using detergent it inactivate viruses (column 3 lines 1-7). One of ordinary skill in the art would have had a reasonable expectation of success of combining these methods because both Kraus et al and Anderle et al were teaching the purification of proteins such as plasma fractions.

M.P.E.P. § 2144 recites, "The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law…If the facts in a prior legal decision are sufficiently similar to those in an application under examination, the examiner may use the rationale used by the court." In *In re Burhans, 154 F.2d 690, 69 USPQ 330* (CCPA 1946), the court found that selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results. In *In re Gibson, 39 F.2d 975, 5 USPQ 230* (CCPA 1930), the court found that selection of any order of mixing ingredients is *prima facie* obvious.

Therefore the combined teachings of Kraus et al and Anderle et al render obvious Applicant's invention as claimed.

Claims 7, 15, 20 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kraus et al (US 5,143,838) in view of Anderle et al (US 2003/0133829) as applied to claims 1-6, 14, 16-19, 21-24 and 26-29 above, and further in view of Kingdom et al (US 5,354,682) and Heimburger et al (US 6,346,277).

Claim 7 is drawn to the method of claim 6 further comprising the steps of f) passing the product of step e) through a filter which retains pathogens, step g) adding a divalent metal ion and a carbohydrate to the product of step f), step h) freeze-drying and heat-treating the product of step g) to inactivate viruses.

Claim 15 is drawn to the method of claim 14, further comprising the steps of g) passing the product of step f) through a filter which retains pathogens, h) adding a divalent metal ion and a carbohydrate to the product of step g), step i) freeze-drying and heat-treating the product of step h) to inactivate viruses.

The combined teachings of Kraus et al and Anderle et al render obvious Applicant's invention as claimed as described above. Heat treatment is suggested by Kraus et al as a suitable method for sterilization of the thrombin product (column 3 lines 1-7).

Kingdom et al teach that after elution from a capture means thrombin may be further processed through lyophilization, ultrafiltration and other conventional methods.

Stability of the final thrombin product is enhanced by infusion of starch, dextran, or combinations thereof (carbohydrates) and packaged for drug use (column 5 line 64-column 6 line 7).

Heimburger et al teach that to destroy the hepatitis viruses in a blood plasma fraction it is beneficial to add calcium ions and sucrose to a blood plasma fraction prior to heat treatment to increase the stability of the final product (column 5 lines 25-30). The product subject to this treatment can also be supplied in freeze-dried form as well (column 6 lines 34-40).

Therefore one of ordinary skill in the art would have been motivated to freeze–dry the thrombin product because Kingdom et al teach that it is suitable to do so and would have allowed the thrombin to be stored for long periods of time. One of ordinary skill in the art would have been motivated to add agents (such as carbohydrates) to enhance the stability of the thrombin product because Kingdom et al suggests that it is beneficial to do so. One of ordinary skill in the art would have been motivated to add calcium ions with a carbohydrate such as sucrose because Heimburger et al teach that these agents will increase the stability of a blood plasma fraction upon heat treatment for the killing of hepatitis viruses and because Kraus et al suggests that it is beneficial to heat treat thrombin. One of ordinary skill in the art would have had a reasonable expectation of success because the references are all drawn to increasing the sterility and stability of blood plasma fractions and because Kingdom et al teach that conventional methods may be used to further process the thrombin product.

Therefore the combined teachings of Kraus et al, Anderle et al, Kingdom et al and Heimburger et al render obvious Applicant's invention as claimed.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA SCHUBERG whose telephone number is (571)272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford/
Primary Examiner, Art Unit 1651